ANESTHESIOLOGY

Mild Acute Kidney Injury after Noncardiac Surgery Is Associated with Long-term Renal Dysfunction

A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Perioperative acute kidney injury is common
- It is unclear whether this merely represents a transient increase in creatinine or has prognostic value

What This Article Tells Us That Is New

- Patients with mild postoperative kidney injury (stage I) after noncardiac surgery had estimated 2.4 times higher odds of having long-term renal dysfunction compared with patients without postoperative kidney injury
- A quarter of patients who had stage I acute kidney injury postoperatively still had stage I kidney injury 1 to 2 yr later, and an additional 11% had even worse renal function

ABSTRACT

Background: Perioperative acute kidney injury is common. However, it is unclear whether this merely represents a transient increase in creatinine or has prognostic value. Therefore, the long-term clinical importance of mild postoperative acute kidney injury remains unclear. This study assessed whether adults who do and do not experience mild kidney injury after noncardiac surgery are at similar risk for long-term renal injury.

Methods: This study is a retrospective cohort analysis of adults having noncardiac surgery at the Cleveland Clinic who had preoperative, postoperative, and long-term (1 to 2 yr after surgery) plasma creatinine measurements. The exposure (postoperative kidney injury) and outcome (long-term renal injury) were defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) initiative criteria. The primary analysis was for lack of association between postoperative kidney injury (stage I *vs.* no injury) and long-term renal injury.

Results: Among 15,621 patients analyzed, 3% had postoperative stage I kidney injury. Long-term renal outcomes were not similar in patients with and without postoperative stage I injury. Specifically, about 26% of patients with stage I postoperative kidney injury still had mild injury 1 to 2 yr later, and 11% had even more severe injury. A full third (37%) of patients with stage I kidney injury therefore had renal injury 1 to 2 yr after surgery. Patients with postoperative stage I injury had an estimated 2.4 times higher odds of having long-term renal dysfunction (KDIGO stage I, II, or III) compared with patients without postoperative kidney injury (odds ratio [95% CI] of 2.4 [2.0 to 3.0]) after adjustment for potential confounding factors.

Conclusions: In adults recovering from noncardiac surgery, even small postoperative increases in plasma creatinine, corresponding to stage I kidney injury, are associated with renal dysfunction 1 to 2 yr after surgery. Even mild postoperative renal injury should therefore be considered a clinically important perioperative outcome.

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Both the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE)[1] and the Kidney Disease: Improving Global Outcomes (KDIGO)[2] stages of acute kidney injury (AKI) are defined in terms of creatinine increase and urine output. Both are well validated in medical patients. For example, AKI reportedly prolongs hospitalization and increases readmissions; it is also associated with increased healthcare costs, sepsis, and mortality.[3–10] However, most of the data regarding outcomes of AKI originate from cohorts of hospitalized medical patients, patients admitted to critical care units, or trauma victims.

By convention—but without other justification—postoperative kidney injury is defined in terms of creatinine alone. One difficulty is that creatinine can increase after surgery because of dehydration or surgical muscle injury, neither of which would necessarily have any prognostic importance. A further difficulty is that nearly all postoperative AKI is stage I, which mostly represents "risk" rather than injury; stage II injury is uncommon, and stage III injury is rare. Nonetheless, the three stages are generally combined into a composite of "acute kidney injury," ignoring the obvious differences in incidence and severity across

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the three degrees of injury. Examples include studies evaluating the associations between various exposures and postoperative AKI including intraoperative hypotension,[11,12] perioperative anemia,[13] and preoperative use of clonidine or aspirin.[14]

Postoperative acute kidney injury affects 7 to 13% of the 300 million patients undergoing surgery each year.[12,15–18] Risk is similar after cardiac and major abdominal surgery.[15] Postoperative AKI is associated with increased risk of various short- and long-term complications, but whether AKI mediates the risk remains unclear.[19] Similarly, patients with postoperative AKI appear to have increased mortality,[20–25] but this evidence relies on various definitions of AKI, usually considering advanced and severe renal injury.

We therefore evaluated the long-term consequences of mild postoperative AKI, with the expectation that there would be no difference in long-term renal outcomes between those with stage I postoperative AKI and those with no postoperative AKI. The goal of the study was to describe renal status and mortality of surgical patients suffering various degrees of postoperative AKI 1 to 2 yr after surgery. We also tested the primary hypothesis that adults with and without stage I postoperative AKI are at similar risk of long-term renal injury. Secondarily, we tested for similarity on 2-yr mortality in patients with and without postoperative stage I AKI.

Materials and Methods

With approval from the Cleveland Clinic institutional review board (Cleveland, Ohio) and waived informed consent, we conducted a retrospective analysis of adults 18 to 85 yr old who had noncardiac surgery at the Cleveland Clinic Main Campus between January 2005 and December 2015 and remained hospitalized at least one night. To limit attrition bias, we only included patients whose primary address was within one of the seven counties surrounding the Cleveland Clinic (Cuyahoga, Lorain, Medina, Summit, Portage, Geauga, and Lake). Surgeries were included only when patients had plasma creatinine measured during the 3 preceding months, during the initial 7 postoperative days, and between 1 and 2 yr after surgery.

We excluded patients with preoperative chronic kidney disease (appendix 1), sepsis, and surgeries of the genitourinary system (appendix 2). We also excluded surgeries if another surgery occurred during the initial postoperative year unless renal injury already existed before the succeeding surgery or if this succeeding surgery was planned to address a new renal injury (*e.g.*, arteriovenous fistula to promote hemodialysis; fig. 1).

We defined the exposure groups by the degree of postoperative kidney injury, according to the KDIGO initiative criteria.[2] As previously modified by Walsh and colleagues,[12] we ignored urine output and extended the postoperative window for capturing the highest measured creatinine concentration to 7 days to better characterize the postoperative period.[2] We then compared the highest creatinine concentration in the week after surgery to the most recent preoperative concentration. For analytical purposes, we *a priori* decided to combine stages II and III AKI.

Our primary outcome was long-term renal injury, defined by the difference between the highest available creatinine level during the period between 1 and 2 yr from surgery and the preoperative concentration closest to surgery. Long-term renal outcome was staged according to similar thresholds adopted from the KDIGO criteria: no renal injury (creatinine increase of less than 0.3 mg/dl and less than 1.5 times the baseline); mild injury (creatinine increase of at least 0.3 mg/dl or 1.5 to 1.9 times the baseline level); moderate injury (creatinine 2.0 to 3.0 times the baseline); or severe injury (increase to greater than 3.0 times baseline or creatinine level of at least 4 mg/dl or dependency on renal replacement therapy). Even though we reported long-term renal injury by stage, formal analysis was based on binary outcome and included anyone with mild or more serious long-term renal injury.

Missing confounder values (comorbidities [0.1%], race [0.02%], baseline hemoglobin [0.3%], body mass index [0.3%], and smoking status [2%]) were imputed by multivariable imputation with five imputation data sets using the SAS procedures PROC MI and PROC MIANALYZE to aggregate results across the five imputed data sets. The imputation model was based on all the variables listed in table 1 together with mortality and preoperative 7-day and 1- to 2-yr postoperative creatinine levels.

For the primary hypothesis, we tested for a lack of association (*i.e.*, similarity or equivalence) between the two study groups (postoperative stage I AKI *vs.* no postoperative AKI) on long-term renal injury. We *a priori* defined a minimal clinically important difference as greater than 20% relative difference in odds of the outcome between groups. Our choice of Δ was based on clinical judgement.

We built multivariable logistic regression models with 1- to 2-yr renal injury status as the outcome variable. The resulting odds ratio estimates the relative odds of long-term injury (KDIGO stage I, II, or III) in the stage I AKI group *versus* patients without postoperative AKI. The logistic regression model was adjusted for the predefined potential confounding variables listed in table 1. The corresponding odds ratio and 95% CIs are reported. We would therefore only claim no association (*i.e.*, stage I postoperative AKI patients having similar odds of long-term renal injury as patients with no postoperative AKI) if the 95% CI of the odds ratio were between 0.83 and 1.2 (corresponding to $\pm$20% fold change in the log odds of the outcome; odds ratios of 0.83 and 1.2 are symmetric at about 1.0 on the log scale).

We performed a *post hoc* sensitivity analysis similar to the primary analysis while including only elective surgeries. We also conducted a *post hoc* sensitivity analysis using time-to-event modeling approach to account for variations in follow-up times between patients. Particularly, the relationship

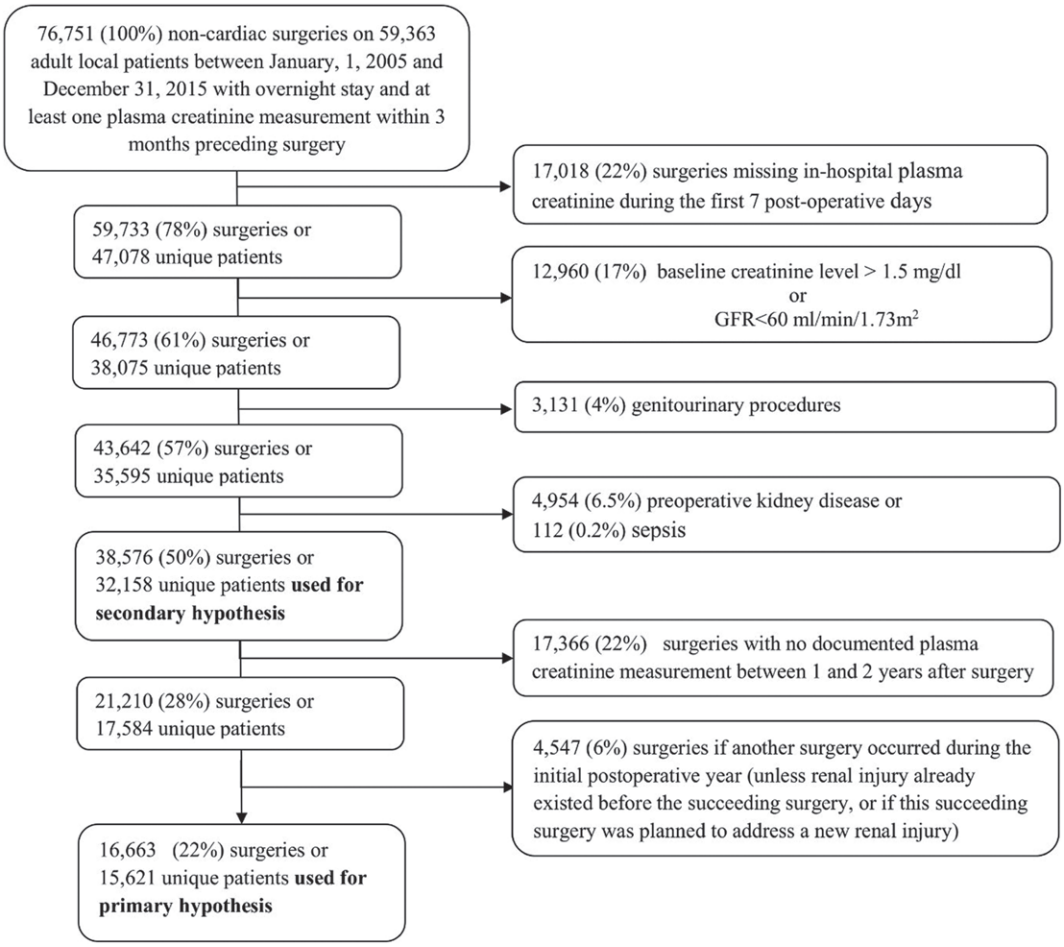

Fig. 1. Enrollment flow chart. GFR, glomerular filtration rate.

between postoperative kidney status and long-term kidney outcome was analyzed using a multivariable Cox proportional hazards regression model, adjusting for all predefined potential confounding variables as in the primary analysis. Patients were censored at the time of their last documented creatinine concentration.

Our secondary hypothesis was assessed by testing for no association (*i.e.*, similarity or equivalence) between mild postoperative kidney injury (postoperative stage I AKI *vs.* no postoperative AKI) and mortality within 2 yr after surgery using survival analysis. We performed survival analysis on a larger cohort of 32,158 patients, including the patients who did not have 1- to 2-yr follow-up creatinine recorded (fig. 1). Incomplete mortality data were observed for patients who were alive or lost to follow-up at the time of the analysis; these patients were censored at their last follow-up visit to Cleveland Clinic.

Specifically, the relationship between postoperative kidney status and mortality was analyzed using a multivariable Cox proportional hazards regression model, appropriate for censored time-to-event outcomes, adjusting for the predefined potential confounding variables listed in table 1. The assumptions of proportional hazards were assessed graphically; the hazard ratios and 95% CIs are reported. The hypothesis was evaluated by testing whether or not the hazard ratio for mortality corresponding to postoperative AKI status (stage I AKI *vs.* no AKI) was within predefined boundaries. Lack of association (*i.e.*, similarity) was concluded at the significance level of 0.05 if the limits of the 95% CI were between 0.83 and 1.2 in ratio of hazards, which corresponded to ±20% change in the log hazards of mortality.

After considering the original study results, we also performed *post hoc* comparisons to determine whether postoperative stage I AKI is associated with better long-term primary and secondary outcomes than postoperative stage II and III AKI. We constructed multivariable logistic regression and multivariable Cox proportional hazards regression models analogous to the primary and secondary analyses and reported model-based *P* values and estimates along with 95% CIs.

Table 1. Demographic, Baseline, and Surgical Characteristics by Postoperative Kidney Injury Stage (N = 15,621)

Factor	Total (N = 15,621)	No AKI (N = 15,022)	AKI Stage I (N = 523)	AKI Stage II or III (N = 76)
Baseline characteristics				
Age, yr*†	57 ± 14	57 ± 14	61 ± 13	57 ± 11
Race, N (%)*†				
White	11,967 (77)	11,552 (77)	358 (69)	57 (76)
Black	3,302 (21)	3,133 (21)	155 (30)	14 (19)
Other	308 (2)	297 (2)	7 (1)	4 (5)
Female, N (%)*†	9,284 (60)	9,002 (60)	241 (46)	41 (55)
Body mass index, kg/m²*†	31 ± 9	31 ± 9	32 ± 9	31 ± 8
ASA Physical Status*†				
I	194 (1)	191 (1)	2 (0)	1 (1)
II	4,839 (31)	4,733 (32)	92 (18)	14 (19)
III	9,439 (61)	9,044 (60)	351 (68)	44 (59)
IV and V	1,118 (7)	1,027 (7)	75 (14)	16 (21)
Risk stratification index*†	–0.5 ± 1.6	–0.5 ± 1.5	0.27 ± 2.2	1.1 ± 2.9
Medications, N (%)				
Aspirin*	1,453 (9)	1,392 (9)	51 (10)	10 (13)
Nonsteroidal antiinflammatory agents*	1,669 (11)	1,619 (11)	44 (8)	6 (8)
Calcium channel blockers	1,162 (7)	1,087 (7)	66 (13)	9 (12)
β Blockers	2,198 (14)	2,078 (14)	109 (21)	11 (15)
Diuretics*	1,810 (12)	1,703 (12)	95 (18)	12 (16)
Angiotensin-converting enzyme inhibitors*	1,440 (9)	1,343 (9)	84 (16)	13 (17)
Angiotensin II receptor blockers*	582 (4)	546 (4)	34 (7)	2 (3)
Statins	1,951 (13)	1,843 (12)	96 (18)	12 (16)
Proton-pump inhibitors	1,889 (12)	1,807 (12)	72 (14)	10 (13)
Immunosuppressants†	94 (1)	86 (1)	7 (1)	1 (1)
Steroids[b]	1,331 (9)	1,290 (9)	34 (7)	7 (9)
Nephrotoxic antineoplastic agents*†	103 (1)	101 (1)	2 (0)	0 (0)
Baseline comorbidities, N (%)				
History of myocardial infarction†	429 (3)	404 (3)	21 (4)	4 (5)
History of congestive heart failure*†	830 (5)	778 (5)	50 (10)	2 (3)
History of peripheral vascular disease*†	1,757 (11)	1,660 (11)	90 (17)	7 (9)
History of stroke*†	945 (6)	904 (6)	36 (7)	5 (7)
Pulmonary circulation disease†	221 (1)	203 (1)	16 (3)	2 (3)
Liver disease*†	1,125 (7)	1,058 (7)	52 (10)	15 (21)
Hypothyroidism†	1,809 (12)	1,743 (12)	58 (11)	8 (11)
Hypertension*†	8,198 (53)	7,799 (52)	357 (69)	42 (58)
Diabetes*†	2,881 (19)	2,696 (18)	163 (32)	22 (30)
Dyslipidemia†	5,414 (35)	5,185 (35)	201 (39)	28 (38)
Smoking*†	2,092 (15)	2,018 (15)	61 (13)	13 (18)
Obesity*†	3,971 (26)	3,788 (25)	161 (31)	22 (30)
Chronic obstructive pulmonary disease†	2,428 (16)	2,319 (16)	90 (18)	19 (26)
Coronary artery disease*†	652 (4)	612 (4)	37 (7)	3 (4)
Atrial fibrillation†	880 (6)	819 (6)	57 (11)	4 (5)
Metastatic cancer*†	1,130 (7)	1,075 (7)	48 (9)	7 (10)
Solid tumor without metastases*†	2,308 (15)	2,187 (15)	103 (20)	18 (25)
Fluid and electrolyte disorders†	2,064 (13)	1,876 (13)	156 (30)	32 (44)
Preoperative				
Preoperative hemoglobin†	13.2 ± 1.8	13.2 ± 1.8	12.7 ± 1.9	12.5 ± 2.1
Number of antihypertensive agents, N (%)*†				
0	10,244 (66)	9,945 (66)	260 (50)	39 (51)
1	2,908 (19)	2,797 (19)	97 (19)	14 (18)
2	1,405 (9)	1,307 (9)	86 (16)	12 (16)
3	1,064 (7)	973 (7)	80 (15)	11 (15)
Surgery characteristics				
Type of surgery, N (%)*†				
Endoscopy/other minor procedures	2,765 (17.7)	2,692 (17.9)	62 (11.9)	11 (14.5)
Abdominal	2,593 (16.6)	2,471 (16.4)	106 (20.3)	16 (21.1)
Orthopedic	2,537 (16.2)	2,419 (16.1)	107 (20.5)	11 (14.5)
Thoracic/vascular	1,285 (8.2)	1,212 (8.1)	64 (12.2)	9 (11.8)
Neurosurgery	1,239 (7.9)	1,216 (8.1)	21 (4.0)	2 (2.6)
Urology	839 (5.4)	808 (5.4)	29 (5.5)	2 (2.6)
Spine	837 (5.4)	822 (5.5)	14 (2.7)	1 (1.3)

(*Continued*)

Table 1. (Continued)

Factor	Total (N = 15,621)	No AKI (N = 15,022)	AKI Stage I (N = 523)	AKI Stage II or III (N = 76)
General surgery	830 (5.3)	794 (5.3)	30 (5.7)	6 (7.9)
Gynecology	680 (4.4)	675 (4.5)	4 (0.76)	1 (1.3)
Others	2,016 (12.9)	1,913 (12.7)	86 (16.4)	17 (22.4)
Emergency surgery, N (%)*†	839 (5)	783 (5)	51 (10)	5 (7)
Duration of surgery, min*†	242 ± 120	241 ± 118	282 ± 141	341 ± 163
Use of regional analgesia, N (%)*	1,846 (12)	1,745 (12)	90 (17)	11 (15)
Use of inotropes/vasopressors, N (%)†				
Ephedrine	6,344 (41)	6,078 (41)	243 (47)	23 (30)
Phenylephrine	8,543 (55)	8,159 (54)	334 (64)	50 (66)
Epinephrine	535 (3)	470 (3)	55 (11)	10 (13)
Norepinephrine	163 (1)	130 (1)	24 (5)	9 (12)
Vasopressin	40 (0)	34 (0)	5 (1)	1 (1)
Estimated blood loss, cc*†	100 [50, 300]	100 [50, 250]	200 [50, 500]	400 [100, 1,550]
Red blood cell transfusion, N (%)*†	1,189 (8)	1,072 (7)	92 (18)	25 (33)
Fresh frozen plasma transfusion, N (%)†	251 (2)	206 (1)	29 (6)	16 (21)
Platelets transfusion, N (%)†	251 (1.6)	202 (1.3)	35 (6.7)	14 (18.4)
Colloids infusion, l[a]	0 [0, 0.5]	0 [0, 0.5]	0.5 [0, 1]	0.5 [0, 1]
Crystalloids infusion, l*	2.4 [1.7, 3.3]	2.4 [1.7, 3.2]	2.8 [1.9, 4.1]	3.1 [2.1, 4.6]
TWA MAP < 65 mmHg (mmHg below 65)* †	0.4 ± 0.7	0.3 ± 0.7	0.5 ± 0.9	0.5 ± 0.8
Postoperative				
Use of postoperative nephrotoxic antibiotics (aminoglycosides), N (%)*	4,649 (30)	4,518 (30)	114 (22)	17 (26)

The data are reported as means ± SD, N (%), or median [interquartile range], as appropriate.

*List of confounders used for adjustment in the all analyses on long-term renal outcome. †List of confounders used for adjustment in the all-analyses 2-yr mortality outcome.

AKI, acute kidney injury; ASA, American Society of Anesthesiologists; TWA MAP, time-weighted average mean arterial pressure.

To evaluate the magnitude of potential attrition bias introduced into our analysis by the exclusion of cases without creatinine levels at 1 to 2 yr, we conducted a *post hoc* exploration comparing the baseline and surgical characteristics of patients used in the analysis and cases who were excluded due to absence of long-term creatinine measurements. We considered all eligible patients between 2005 and 2015. While planning the study, we expected that there would be about 50,000 patients from the 7 counties around Cleveland who had long-term creatinine measurements. Among those, based on our past studies of similar patients, we expected 47,500 patients (95%) would not have postoperative AKI and 1,850 (3.7%) would have postoperative stage I AKI. Assuming we would be able to match 3,200 patients (N = 1,600 patients with stage I AKI), this sample would provide only about 10% power at the 0.05 significance level to detect "no association" (*i.e.,* equivalence) comparing patients with postoperative stage I AKI to patients without postoperative AKI, assuming "equivalence" boundaries for the odds ratio of 0.83 and 1.2, true odds ratio of 1, and incidence of long-term kidney dysfunction among patients without AKI of 0.5%. Recognizing that we most likely would be underpowered on both primary and secondary hypotheses, we continued with the analysis because our main goal was descriptive: to report long-term renal dysfunction and mortality in patients with various degrees of postoperative AKI. We further note that the observed CI for the odds ratio for this association was 2.0 to 3.0, a fairly precise estimate of the relationship of interest. SAS statistical software version 9.4 (SAS Institute, USA) for 64-bit Microsoft Windows was used for all statistical analyses.

Results

Among 59,363 available patients, we were able to analyze data from 15,621 patients. The reasons for exclusion are detailed in figure 1, with missing postoperative or long-term creatinine concentrations and baseline renal dysfunction being the major causes for exclusion.

The incidence of postoperative stage I AKI was 523 (3%). Only 76 (0.5%) patients had stages II or III postoperative AKI. The demographic, baseline, and surgical characteristics of the different groups are detailed in table 1.

Patients with postoperative stage I AKI were not similar to patients with no postoperative AKI in terms of long-term renal injury with an odds ratio (95% CI) of 2.4 (2.0 to 3.0; table 2). Among the 523 patients with postoperative stage I AKI, 194 (37%) still had either mild or moderate-to-severe renal injury 1 to 2 yr after surgery, compared with 14% of those who did not suffer postoperative AKI (fig. 2). The results of the sensitivity analysis of the 14,782 elective surgeries were nearly identical to the primary results with an odds ratio (95% CI) of 2.5 (2.0 to 3.1). The sensitivity analysis using time to event gave similar results: the hazard ratio (95% CI) of the long-term renal dysfunction was 1.9 (1.6 to 2.2) comparing patients with postoperative stage I AKI to patients with no AKI. The *post hoc* analysis comparing stage

Table 2. Long-term (1 to 2 yr) Renal Dysfunction According to Postoperative Degree of Acute Kidney Injury (N = 15,621)

Postoperative Status	Long-term Renal Outcome (Modeled as Any *vs.* None)			
	No Renal Dysfunction	Mild Renal Dysfunction	Moderate to Severe Renal Dysfunction	Adjusted Odds Ratio
No AKI (N = 15,022)	12,974 (86%)	1,575 (11%)	473 (3%)	1.0 (reference)
AKI stage I (N = 523)	329 (63%)	138 (26%)	56 (11%)	2.4 (2.0 to 3.0)*
AKI stages II and III (N = 76)	45 (59%)	22 (29%)	9 (12%)†	

The data are descriptively reported as N (%). The odds ratios were based on multivariable logistic regression modeling of the outcome of any long-term renal injury (mild, moderate, or severe *vs.* no renal dysfunction) as a function of postoperative kidney status, with adjustment for the potential confounding factors listed in table 1.

*The adjusted odds ratio is presented for the primary analysis (association between postoperative stage I AKI *versus* no postoperative AKI on any long-term kidney dysfunction). Interpretation of odds ratio of 2.4: odds of having any long-term (1 to 2 yr postsurgery) kidney injury (mild, moderate, or severe) was an estimated 2.4 times higher for postoperative AKI stage I patients compared to those with no postoperative dysfunction. †The *post hoc* analysis found no significant association when comparing patients with postoperative stage II/III *versus* stage I AKI on renal dysfunction 1 to 2 yr after surgery, with adjusted odds ratio (95% CI) of 1.0 (0.6 to 1.8), $P = 0.94$; significance criterion is $P < 0.05$. Interpretation: there is no significant difference in the risk of kidney injury 1 to 2 yr after surgery between patients with postoperative stage I *versus* stages II/III AKI.

AKI, acute kidney injury.

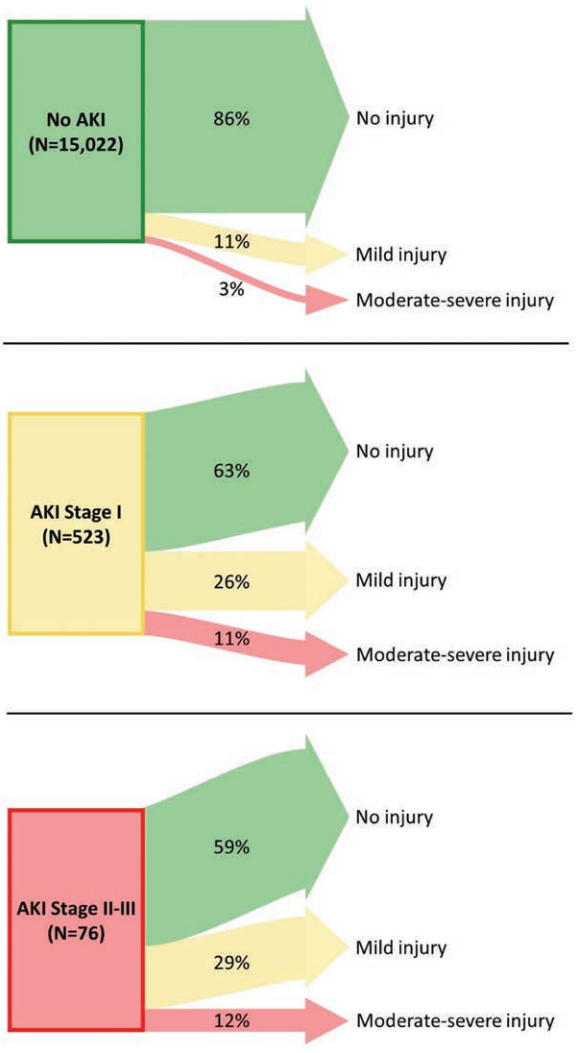

Fig. 2. Renal outcomes 1 to 2 yr after surgery, according to postoperative acute kidney injury (AKI) stage. Width of the *arrows* represents the percentage of patients from each exposure group having each stage of long-term renal injury.

I with stage II/III AKI found no difference in long-term renal outcome, with adjusted odds ratio (95% CI) of 1.0 (0.6 to 1.8; superiority $P = 0.94$; table 2).

For the secondary outcome of 2-yr mortality, we found similarity between AKI status (stage I AKI *vs.* no postoperative AKI) with an estimated hazard ratio (95% CI) of 1.04 (0.93 to 1.16), equivalence $P < 0.025$ for each of lower and upper Δ values, and CI between the predetermined deltas of 0.83 and 1.2 (table 3). The *post hoc* comparison found no difference between stage I *versus* stage II/III postoperative AKI patients on mortality (superiority $P = 0.34$; table 3).

Supplemental Digital Content 1 (http://links.lww.com/ALN/C157) describes the comparison of patients included in the analysis with those who were excluded due to absence of 1- to 2-yr creatinine measurements. Whereas comparable on many characteristics, the included patients were more likely to be older, have worse American Society of Anesthesiologists (ASA) Physical Status score, hypertension, and dyslipidemia.

Discussion

In contrast to our primary hypothesis, we found that more than a quarter of patients with stage I postoperative AKI still had mild renal injury 1 to 2 yr later, and 11% had even worse injury. A full third of the patients with stage I AKI thus had renal injury 1 to 2 yr after surgery, indicating that even mild postoperative creatinine increases are of considerable prognostic importance. Consequently, a diagnosis of postoperative stage I AKI more than doubled the odds of having renal injury 1 to 2 yr after surgery compared with patients who did not have postoperative AKI (fig. 2).

Among patients who had stage II or III postoperative AKI, only 12% were still so categorized 1 to 2 yr later. However, 29% still had mild injury. The long-term prognosis for stage II and III AKI, interestingly, was therefore comparable with stage I AKI. Stage I AKI thus appears to be nearly as predictive of long-term renal dysfunction as more advanced postoperative kidney injury.

Table 3. Mortality according to Postoperative Degree of Acute Kidney Injury (N = 32,158)

	Mortality within 2 Yr after Surgery	Adjusted Hazard Ratio (95% CI)
No AKI (N = 30,974)	2,884 (9%)	1.0 (reference)
AKI stage I (N = 1,029)	161 (16%)	1.04 (0.93 to 1.16)*
AKI stages II and III (N = 155)	26 (17%)†	

The data are descriptively reported as N (%). Hazard ratios were based on multivariable Cox proportional hazards regression model with adjustment for potential confounding factors listed in table 1.

*Presented is the adjusted hazards ratio for the secondary outcome. The mortality was similar between patients with stage I postoperative AKI and patients with no postoperative AKI. Equivalence $P = 0.006$; significance criterion is $P < 0.05$. †The adjusted hazards ratio (95% CI) for the *post hoc* analysis testing for association between postoperative stage I *versus* stage II/III AKI and mortality is 0.86 (0.63 to 1.17), $P = 0.34$; significance criterion is $P < 0.05$. Patients with stage II/III AKI were not at higher mortality risk than patients with stage I AKI.

AKI, acute kidney injury.

Our secondary analysis evaluating mortality demonstrated similarity between patients with postoperative stage I AKI and those with no AKI, with a hazard ratio (95% CI) of 1.04 (0.93 to 1.16). Because the 95% CI is within the predefined equivalence boundaries, the statistical conclusion is that mortality is similar between the two groups. There was also no difference in mortality between stage I and stage II/III postoperative AKI. That postoperative AKI has little or no effect on mortality is perhaps unsurprising because renal failure can be treated safely, at least over a period of years. Nevertheless, these results are based on a relatively small number of deaths and should therefore be considered cautiously.

We selected the widely accepted KDIGO criteria to define both the exposure (acute postoperative kidney injury) and the outcome (renal injury 1 to 2 yr later). The KDIGO grading system was developed by a consensus nephrology group[2] and recently recommended for diagnosis of postoperative kidney injury by the Standardized Endpoints in Perioperative Medicine Group on renal endpoints.[26,27] As in previous perioperative analyses, we extended the relevant time period for capturing increases in plasma creatinine from 48 h after an insult to 7 postoperative days.[12]

The KDIGO staging system was developed to evaluate *acute* kidney injury rather than as a measure of long-term renal function or injury, but using similar criteria facilitated comparisons over time. The inherent assumption in this approach is that patients with a degree of acute postoperative renal dysfunction whose creatinine is similar or greater 1 to 2 yr later are worse off than those who did not have acute kidney injury or in whom injury resolved.

Our study design mandated the inclusion of patients who had creatinine measurements between 1 and 2 yr after surgery. Many patients come to the Cleveland Clinic for specific treatments, often surgical, and then return to their primary healthcare providers for routine long-term follow-up. With only rare exceptions, out-of-area providers are not part of the clinic system, and follow-up laboratory values are unavailable to us. To limit this sort of attrition bias, we restricted our analysis to patients who live in the seven counties surrounding Cleveland. Approximately 70% of Cleveland Clinic surgical patients live in these seven counties and are consequently likely to have their long-term medical follow-up within the Cleveland Clinic network. Any laboratory values obtained within the network were available to us. However, some patients were surely excluded simply because they had their follow-up done outside the Clinic's system, whether having the renal injury or not.

An additional source of attrition is that relatively healthy patients may have had no indication for creatinine assessments 1 to 2 yr postoperatively. Nearly half the otherwise qualifying patients were excluded because creatinine measurements 1 to 2 yr postoperatively were missing. Our *post hoc* analysis verified that these patients were generally similar to those included in our analysis, including very comparable postoperative kidney status, somewhat decreasing concern about attrition bias. However, the included patients did have somewhat higher age and worse ASA Physical Status and were more likely to have hypertension and dyslipidemia.

Finally, our primary analysis used the outcome of worst observed kidney status between 1 to 2 yr postsurgery, thus using somewhat different lengths of follow-up across patients for the actual creatinine value utilized. We did not account for the differing follow-up lengths when analyzing the ordinal AKI outcome. Whereas this may have introduced some bias in the comparisons, we did consistently use the worst creatinine observed 1 to 2 yr after surgery.

In summary, a quarter of patients with stage I postoperative kidney injury (creatinine increase of at least 0.3 mg/dl or 1.5 to 1.9 times the baseline level) still had mild injury 1 to 2 yr later, and 11% had even higher stage injury. A full third of the patients with stage I kidney injury thus had renal injury 1 to 2 yr after surgery. Consequently, patients with postoperative stage I injury were not similar and had an odds ratio (95% CI) of 2.4 (2.0 to 3.0) for having long-term renal injury compared with patients without postoperative kidney injury. We thus conclude that in adults recovering from noncardiac surgery, even a mild postoperative increase in plasma creatinine, corresponding to stage I kidney injury, is associated with worse renal function 1 to 2 yr after surgery and should therefore be considered a clinically important perioperative outcome.

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Competing Interests

The authors declare no competing interests.

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Appendix 1. Excluded Renal Conditions

Renal Conditions Serving as Exclusion Criteria

Estimated glomerular filtration rate < 60 ml × min^{-1} × 1.73 m^{-2}
Baseline plasma creatinine concentration > 1.5 mg/dl
Preoperative diagnosis of kidney disease (International Classification of Disease version 9 codes 580.x 581.x 582.x 583.x 584.x 585.x 586.x 587.x 588.x 590.x 591.x 447.0)

Appendix 2. Excluded Procedures

Procedures Serving as Exclusion Criteria

Operations on the kidney and ureter (International Classification of Disease version 9 codes 55.x, 56.x)
Procedures to promote dialysis (International Classification of Disease version 9 codes 38.95, venous catheterization for renal dialysis; 39.95, hemodialysis, including artificial kidney, hemodiafiltration, hemofiltration, renal dialysis)